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Abstract

Achiral macrobicyclic cleft containing a pyridine ring (**1**) formed a complex at 25 °C in 50% CH_3OH/50% $CHCl_3$ (v/v) with a primary ammonium salt (log K = 3.15) as evidenced by a significant change in the ^{1}H NMR spectrum. Highly organized pyridine-containing macrobicycle (*S,S,S,S*)-**2** exhibited recognition at 25 °C in 20% C_2H_5OH/80% 1,2-$C_2H_4Cl_2$ (v/v) for the (*S*)-enantiomer of α-(1-naphthyl)ethylammonium perchlorate (NapEt) over its (*R*)-form (Δ log$K$ = 0.85). This high recognition factor probably reflects an increase in molecular rigidity by the introduction of a second macroring on the monocyclic pyridinocrown ligand.

Introduction

As reported in our Technical Report number 48,[1] one achiral and two chiral macrobicyclic clefts have been prepared (see Figure 1 for structures). An extensive review of these types of compounds was presented in that report. This report covers the recognition by two of these macrobicyclic hosts for organic ammonium perchlorates.

Results and Discussion

^{1}H NMR spectroscopy gave clear evidence that achiral macrobicycle 1 could function as a host for primary ammonium salts. The addition of one equivalent of (*R*)-(+)-(α-phenylethyl)ammonium perchlorate (PhEt) to a solution of the macrobicycle in a mixture of $CDCl_3$ and CD_3OD (1:1, v:v) resulted in substantial spectral changes. For instance, the doublet arising from the protons in the 3-position of the pyridine ring was shifted up-field from δ 7.538 to δ 7.381. More complex changes were observed in the spectrum reflecting the overall decrease in symmetry of the host-guest complex compared to the free host arising from the chiral nature of the ammonium salt. This could be seen clearly in the region δ 4.05 to δ 4.40 where the AB system, originating from the benzylic methylene protons adjacent to the benzene rings, was split into two distinctly separate AB patterns upon complexation. A log K value of 3.15 (See Table I) for the complexation of (*R*)-(+)-PhEt was determined from the chemical shift changes induced by the incremental addition of the salt, according to the technique described by Zhu *et al.*[2] In a similar manner, the association constants for the binding of (*R*)-(-)-phenylglycinol hydrogen perchlorate (PhEtOH) and (*R*)-(+)-α-(1-naphthyl)ethylammonium perchlorate (NapEt) were found to be 2.95 and 2.32, respectively. The lower value in the latter case probably reflects the bulkier nature of the guest.

Thermodynamic quantities for interactions of macrobicyclic compounds **1**, (*S,S,S,S*)-**2** and dimethylpyridino-18-crown-6 ligand (*S,S*)-**3** with three primary organic ammonium salts are listed in Table 1. The ligands and ammonium salts are shown in Figure 1. Compared with (*S,S*)-**3**, macrobicyclic (*S,S,S,S*)-**2** shows improved enantiomeric recognition towards NapEt. A large difference in stabilities between the complexes of (*R*)- and (*S*)-NapEt with (*S,S,S,S*)-**2** ($\Delta \log K$ = 0.85) is observed in a 2:8 (v/v) EtOH/ClC_2H_4Cl (2Et/8DCE) solvent mixture, while the $\Delta \log K$ value for (*R*)- and (*S*)-NapEt interactions with (*S,S*)-**3** is 0.46 in the same solvent mixture. The $\Delta \log K$ value of 0.85 indicates an excellent enantiomeric recognition. This high degree of enantiomeric recognition by (*S,S,S,S*)-**2** is probably due to an increase in molecular rigidity by introducing a second macroring and two phenyl groups. Thermodynamic data provide evidence for this point. Positive values of entropy changes for **2**-NapEt interactions, as compared with **3**-NapEt interactions which show negative values of entropy changes, suggest a smaller conformational change of ligand **2** during complexation, indicating that **2** is more rigid than **3**.

It is interesting to note that (*S,S,S,S*)-**2** recognizes the (*S*) forms of NapEt and PhEt over their (*R*) forms, a reverse sequence of recognition as compared to (*S,S*)-**3** which recognizes the (*R*) forms of NapEt and PhEt over their (*S*) forms (see Table 1). Both enthalpic and entropic effects make contributions to the enantiomeric recognition of NapEt by (*S,S,S,S*)-**2**. The ΔH and $T\Delta S$ values for (*S*)-NapEt-(*S,S,S,S*)-**2** interaction are 2.1 and 2.75 (kJ/mol), respectively, more favorable than those for (*R*)-NapEt-(*S,S,S,S*)-**2** interaction. On the other hand, only enthalpy change contributes to enantiomeric recognition of NapEt by (*S,S*)-**3**. The ΔH value for (*R*)-NapEt-(*S,S*)-**3** interaction is 1.2 (kJ/mol) more favorable but the $T\Delta S$ value is 0.4 (kJ/mol) more unfavorable than those for (*S*)-NapEt-(*S,S*)-**3** interaction.

As has been observed in other chiral recognition systems, solvent has an effect on enantiomeric recognition with (*S,S,S,S*)-**2**. In MeOH/$CHCl_3$ solvent mixtures, the degree of enantiomeric recognition is lower than that in the 2Et/8DCE binary solvent. A high degree of enantiomeric recognition towards NapEt by (*S,S,S,S*)-**2** is observed in 2Et/8DCE while in 2:8 (v/v) $CD_3OD/CDCl_3$ (2M/8C) the $\Delta\log K$ value decreases to 0.45 and it further decreases to 0.38 with an increase in the $CDCl_3$ component of the solvent mixture (5M/95C). The recognition of (*S,S,S,S*)-**2** for PhEt enantiomers is not directly comparable with that of (*S,S,*)-**3** due to the different solvents used. As seen in Table 1, however, (*S,S,S,S*)-**2** does not show a significant improvement in enantiomeric recognition towards PhEt.

In MeOH, the interaction of macrobicycles **1** and **2** with NapEt and PhEt is very weak. No complexation could be detected by the ^1H NMR spectral method. In the solvent mixtures used, 1M/1C and 2Et/8DCE, **1** and **2** form complexes with NapEt, PhEt, and PhEtOH but the complex stabilities are lower than those with **3**. This observation indicates that the second macroring attached through the two phenyl groups and a enlargement of the pyridine-containing macroring (from 18 members of **1** to 20 members for **1** and **2**) may result in a macrocyclic conformation which weakens tripod hydrogen bonding formed with the ammonium cations. The smaller $-\Delta H$ values for (*R*)- and (*S*)-NapEt interactions with (*S,S,S,S*)-**2** than those for (*R*)- and (*S*)-NapEt interactions with (*S,S*)-**3** support this explanation.

Determination of Thermodynamic Quantities. The $\log K$ values in Table 1 were determined at 25.0 ±0.1 °C by either a direct ^1H NMR titration procedure at 200 MHz or titration calorimetry using a Tronac Model 450 calorimeter. The experimental techniques for direct ^1H NMR[2,5,6] and calorimetric[2,4] titrations have been described in detail. The calorimetric method deterined ΔH and ΔS values besides the $\log K$ values and these values are also reported in Table 1.

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Table I. Log K, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) Values[a] Determined by ^1H NMR and Calorimetric Titrations for Interactions of Chiral Macrocyclic Ligands with Enantiomers of Three Primary Ammonium Cations[b] in Various Solvents at 25 °C.

ligand	cation	log K	ΔH	$T\Delta S$	Δlog K[c]	solvent[d]
1	(*R*)-NapEt	2.32 ± 0.05				1M/1C
	(*R*)-PhEt	3.15 ± 0.05				1M/1C
	(*R*)-PhEtOH	2.95 ± 0.04				1M/1C
(*S,S,S,S*)-2	(*R*)-NapEt	ND				M
	(*S*)-NapEt	ND				M
	(*R*)-PhEt	ND				M
	(*S*)-PhEt	ND				M
	(*R*)-NapEt	2.49 ± 0.05	-13.6 ± 0.8	0.61		2Et/8DCE
	(*S*)-NapEt	3.34 ± 0.04	-15.7 ± 0.7	3.36	0.85	2Et/8DCE
	(*R*)-NapEt	2.26 ± 0.03				2M/8C
	(*S*)-NapEt	2.71 ± 0.03			0.45	2M/8C
	(*R*)-NapEt	2.47 ± 0.04				5M/95C
	(*S*)-NapEt	2.85 ± 0.02			0.38	5M/95C
	(*R*)-PhEt	2.48 ± 0.05				?
	(*S*)-PhEt	2.65 ± 0.05			0.17	?
	(*R*)-PhEt	1.77 ± 0.06				1M/1C
	(*S*)-PhEt	2.10 ± 0.04			0.33	1M/1C
(*S,S*)-3	(*R*)-NapEt[e]	2.47 ± 0.02	-27.6 ± 0.1	-18.9		M
	(*S*)-NapEt[e]	2.06 ± 0.02	-26.4 ± 0.1	-18.5	0.41	M
	(*R*)-NapEt	3.88 ± 0.03	-29.2 ± 0.4	-7.00		2Et/8DCE
	(*S*)-NapEt	3.42 ± 0.04	-23.5 ± 0.7	-3.98	0.46	2Et/8DCE

Table I. (continued)

ligand	cation	log K	ΔH	$T\Delta S$	Δlog K [c]	solvent[d]
(*S*,*S*)-3	(*R*)-NapEt[f]	2.96 ± 0.02				1M/1C
	(*S*)-NapEt[f]	2.43 ± 0.04			0.53	1M/1C
	(*R*)-PhEt[g]	2.33 ± 0.05				M
	(*S*)-PhEt[g]	2.11 ± 0.05			0.22	M

[a] Log K values without ΔH and $T\Delta S$ values were determined using the ^{1}H NMR method. ND means not determined because no significant chemical shift change was observed.

[b] Perchlorate salts of the ammonium cations were used. The notations of ammonium cations are defined in Figure 2.

[c] The Δlog K value is the difference between log K values for enantiomer interactions with a given chiral macrocyclic ligand.

[d] M = methanol; C = chloroform; DCE = 1,2-dichloroethane; Et = ethanol. Solvent mixtures are indicated by volumetric ratios of their components. For example, 1M/1C = 50% methanol-50% chloroform (v/v). For NMR measurements, 100% deuterated solvents were used.

[e] Ref 3.

[f] Ref 4.

[g] Ref 5.

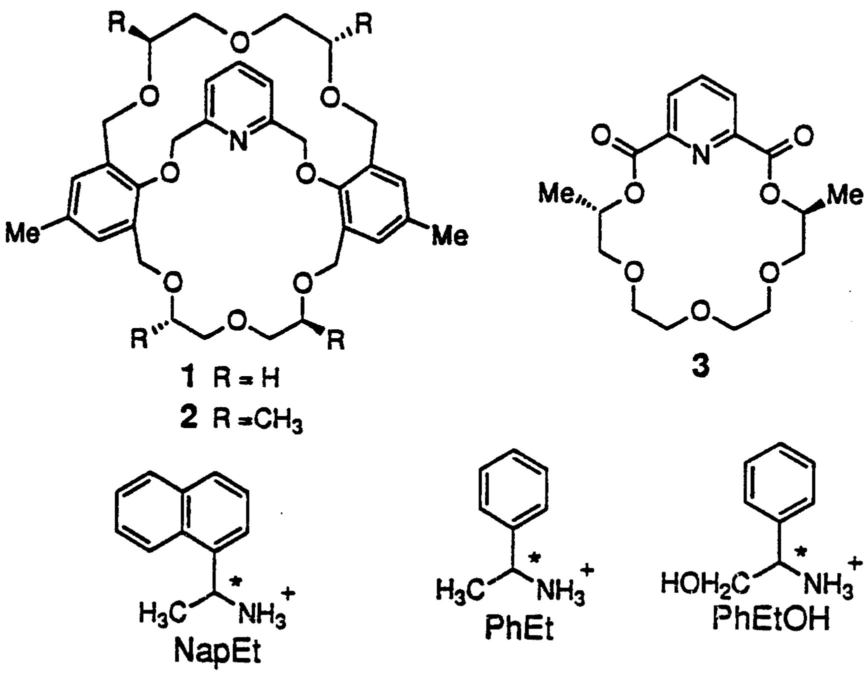

Figure 1. Macrocyclic ligands and chiral organic ammonium perchlorates used in this study.